REMARKS

The applicants acknowledge the withdrawal of rejections under 35 U.S.C. § 102(b) and 35 U.S.C. § 103 pertaining to claims 24-32 with the cancellation of these claims without prejudice or disclaimer. Pending claims 14-22 and 33-38 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Gijbels *et al.* (1995) in view of Vink *et al.* (1990), and further in view of U.S. Patent No. 5,605,930 (Samid). This is the sole outstanding rejection of the claims, and the rejection is respectfully traversed. The applicants also respectfully traverse the finality of the Office action mailed March 11, 2003, as the Office introduced a new rejection not advanced in the previous Office action.

The applicants respectfully traverse the finality of the Office action mailed March 11, 2003 because the rejection under Samid was not advanced in the previous Office action mailed May 30, 2002. As citing Samid presented a new ground for a rejection in the Office action mailed March 11, 2003, it is respectfully requested that the finality be withdrawn.

The rejection of claims 14-22 and 33-38 is respectfully traversed because the combination of Gijbels with Vink or Samid fails to support a *prima facie* case of obviousness. Specifically, the cited combinations fail to teach or suggest the claimed methods for treating a sensitized T-cell-mediated disease by administering an antibody directed against interleukin-6 (IL-6) receptor. There also was no reasonable expectation for successfully arriving at the claimed methods and there was no motivation for combining the cited documents.

There is No Teaching or Suggestion of the Claimed Methods

For the claims to be obvious the cited documents must teach or suggest a method of treating a sensitized T-cell-mediated disease by administering an antibody directed against IL-6

receptor. As Gijbels discusses a method of administering an antibody directed against IL-6 itself, not the IL-6 receptor, there must be some indication in the cited documents that the antibody used in Gijbels could be replaced by an antibody directed against the IL-6 receptor. Alternatively, there must be some indication that a person of ordinary skill in the art would have applied an antibody directed against the IL-6 receptor, an antibody that neutralizes IL-6, to a method of treating a sensitized T-cell-mediated disease. Stated another way, the documents should teach or suggest that a person of ordinary skill in the art would have treated a sensitized T-cell-mediated disease by neutralizing IL-6. The applicants respectfully assert that the cited documents fail to teach or suggest these features, as described hereafter.

The Office's assertion began with the following description in Gijbels:

> The conclusion from these studies is that Abs to IL-6 are protective by neutralizing endogenous IL-6 activity, and hence that IL-6 has a pro-inflammatory affect in these models.

This statement does not by itself teach or suggest an antibody directed against IL-6 receptor would elicit a protective response. Also, it should be noted that the Office failed to quote the next sentence in Gijbels. This next sentence demonstrates that the data in the document was inconclusive as to whether neutralizing IL-6 lead to the observed protective effect in the EAE model:

> However, there have been reports of increased levels of circulating IL-6 after administration of mAb to IL-6 in animals in which IL-6 production was produced . . . in a patient with plasma cell leukemia after anti-IL-6 treatment. We found increased levels of IL-6 bioactivity in serum of animals treated with mAb to IL-6 (emphasis added).

As can be seen, the description cited by the Office is not a conclusion. Rather, Gijbels acknowledges that blood IL-6 concentrations are increased after administration of an anti-IL-6

antibody, and cannot conclude that inhibition of autoimmune disease and inflammation is accomplished simply by neutralizing IL-6 activity. This interpretation is supported by a statement in the abstract on page 795:

> Our study indicates that IL-6 plays an important role in autoimmune CNS inflammation. However, due to the complex nature of the *in vivo* interactions of administered antibodies, the disease-reducing effect of the anti-IL-6 antibodies could be caused by neutralization of IL-6 activity or by enhancement of IL-6 activity via induction of higher IL-6 levels in the CNS. (Emphasis added)

Gijbels concludes on page 804, left column, first paragraph:

> The net result of administration of Ab to a cytokine thus dependent on the balance between two opposing effects (*i.e.*, neutralization and accumulation). These findings indicate that the mechanisms underlying *in vivo* effect of antibodies to cytokines are complex (emphasis added).

As can be seen from these quotations from Gijbels, it could not be concluded that EAE would be treated by neutralizing IL-6 activity since the document could not rule out the possibility a protective response was effected by higher concentrations of IL-6 in the blood. Therefore, it is not obvious from Gijbels that administering an anti-IL-6 receptor antibody would have been effective for treating a sensitized T-cell-mediated disease.

Vink does not cure the defects of Gijbels with respect to the claimed methods. Specifically, Vink does not teach that administering an anti-IL-6 receptor antibody which neutralizes IL-6 could treat a sensitized T-cell-mediated disorder since the document is directed to treating plasmacytoma, a disease of plasma B-cells, not T-cells.

Vink also fails to indicate that the an antibody directed to IL-6 itself can be exchanged for an antibody directed to IL-6 receptor. For such an indication, the document would need to

establish the two antibodies share common properties, and do not exert opposite effects. Vink actually teaches the latter - that the antibodies exert opposite effects in cells. Specifically, Vink teaches on page 999, right column, that the anti-IL-6 receptor antibody 15A7 induced partial necrosis of some tumors, while the anti-IL-6 antibody had no significant effect under the same experimental conditions. Thus, the applicants do not understand the Office's assertion that Vink teaches the antibodies are interchangeable.

There are at least three conclusions from this analysis. First, the Office has not presented or considered the full teachings of Gijbels since it quoted only one-sided portions of the document. Other portions of the document must be considered to understand its full teachings. The proper conclusion from Gijbels is there was no indication that administering an agent which neutralizes IL-6 could be used to treat a sensitized T-cell-mediated disorder. Second, because Gijbels is inconclusive as to whether treatment of EAE can be accomplished by neutralizing IL-6, there is no teaching or suggestion in Gijbels that neutralizing IL-6 with an anti-IL-6 receptor antibody would treat a sensitized T-cell-mediated disease. Third, because Vink shows that an antibody directed against IL-6 receptor and an antibody against IL-6 itself are not interchangeable, Vink does not remedy the defects of Gijbels and the combination does not teach or suggest the claimed methods.

In addition to the combination of Gijbels and Vink, the Office also cited the combination of Gijbels and Samid for the rejection of claims 34-38. The Office alleged that Samid links abnormal expression of IL-6 with pathogenesis and/or symptoms of a variety of diseases. Samid, however, fails to teach that IL-6 expression is involved with the pathogenesis and/or symptoms of sensitized T-cell-mediated diseases. Accordingly, there is no teaching or suggestion of the claimed subject matter by the combination of Gijbels and Samid.

There is No Reasonable Expectation for Successfully Arriving at the Claimed Methods

Gijbels is inconclusive as to whether EAE can be treated by neutralizing IL-6, as explained in the previous section. Vink also is inconclusive as to whether an antibody directed against IL-6 can be replaced by an antibody directed against IL-6 receptor. Accordingly, there was no reasonable expectation for successfully treating a sensitized T-cell-mediated disease by administering an antibody directed against IL-6 receptor to a subject. Thus, if the Office was basing its obviousness rejection on the premise that it would have been obvious to try to treat a sensitized T-cell-mediated disease by administering an antibody directed against IL-6 receptor, this rationale cannot properly support a *prima facie* case of obviousness because there was no reasonable expectation for successfully arriving at that treatment. This point was advanced in the amendment filed December 2, 2002 by the applicants, and is respectfully requested that the Office reconsider the obviousness rejection.

There was no Motivation to Combine the Cited Documents

The applicants respectfully asserted in the amendment filed December 2, 2002 that there was no motivation to combine the cited documents based upon the rationale set forth in *In re Rouffet*, 47 USPQ.2d 1453 (Fed. Cir. 1998). The Office countered this rational in the Office action mailed March 11, 2003, arguing that Gijbels showed IL-6 was neutralized. As explained above, this conclusion is not present in Gijbels as the data in that document was inconclusive as to whether IL-6 was neutralized, and whether neutralization of IL-6 lead to the protective response. Accordingly, the applicants respectfully request that the Office reconsider the applicant's analysis in connection with *In re Rouffet* in the amendment filed December 2, 2002.

The applicants also respectfully request that the Office consider withdrawing the obviousness rejection in view of the reasoning extended in *In re Lalu*, 747 F.2d 703,

223 USPQ 1257 (Fed. Cir. 1984). In *In re Lalu*, the Court of Appeals for the Federal Circuit stated that an element in determining obviousness is the motivation of one having ordinary skill in the art to make and use a composition. The Court noted that "the motivation is not abstract, but practical, and is always related to the properties or uses" one skilled in the art would expect from a composition if made. Here, the person of ordinary skill in the art did not expect that the antibody directed against IL-6 utilized in Gijbels would have the same properties and uses as the antibodies directed against the IL-6 receptor discussed in Vink. Vink utilized the antibodies directed against IL-6 receptor for the purpose of treating plasmacytoma, which is a disease of plasma B cells not sensitized T cells, only the latter of which is claimed. Accordingly, the person of ordinary skill in the art would not have expected that antibodies used to treat diseases of plasma B cell would be useful for treating diseases of sensitized T cells.

Further, Vink failed to show that antibodies directed against IL-6 itself, which were utilized in Gijbels, could be exchanged for antibodies directed against IL-6 receptor because the latter induced partial necrosis of some tumors and the former had no significant effect under the same experimental conditions. Thus, the person of ordinary skill in the art had no motivation to substitute the antibodies described in Vink with the antibodies discussed in Gijbels.

Extending the rationale in *In re Lalu* to the combination of Gijbels and Samid, Samid fails to suggest that IL-6 expression levels are pertinent to T-cell-mediated diseases. Thus, the person of ordinary skill in the art had no reason to apply any of the teachings in Samid to teachings in Gijbels or Vink because each of the documents discusses different types of diseases.

Accordingly, there was no motivation to combine the cited documents.

CONCLUSIONS

The documents cited by the Office, taken alone or in combination, fail to support a *prima facie* case for obviousness with respect to pending claims 14-22 and 33-38. Vink showed there was no reasonable expectation that antibodies directed against IL-6 itself could be exchanged for antibodies directed against IL-6 receptor. Further, in order to expect that antibodies directed against the IL-6 receptor would be useful for treating the EAE disorder described in Gijbels, Gijbels should have shown that EAE was treated by neutralizing IL-6. Because data in Gijbels was inconclusive as to whether EAE was treated by neutralizing IL-6, there was no teaching or suggestion by the cited combination of treating EAE using a antibody directed against IL-6 receptor. It follows that the cited documents did not provide a reasonable expectation for successfully practicing the claimed subject matter. There also was no motivation to combine the cited documents under the reasoning set forth in *In re Rouffet* and *In re Lalu*. Thus, a *prima facie* showing of obviousness cannot be founded upon the cited documents and the applicants respectfully request that the Office withdraw the remaining rejection of the pending claims.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing Docket No. 350292000800.

Respectfully submitted,

Dated: September 11, 2003 By: _____

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